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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,901	FUJIWARA ET AL.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 09/14/2007 has been entered. Claims 1-3 were cancelled. Claims 4-11 are pending. Claims 4, 5, 8, and 11 are amended. Claims 4-11 are currently under examination.

This application 10/520,901 is a 371 of PCT/JP03/08573 07/07/2003 claims the foreign priority of JAPAN 2002-198941 filed on 07/08/2002. Preliminary claim amendments filed on 01/07/2005 have been entered.

Priority

1. This application is a 371 of PCT/JP03/08573 filed 07/07/2003 claims the foreign priority of JAPAN 2002-198941 filed on 07/08/2002. A certified copy of the English translation of JAPAN 2002-198941 filed on 07/08/2002 was provided on 09/14/2007 for instant application. A certified copy of the English translation of JAPAN 2002-198941 filed on 07/08/2002 has been fully considered, and the support for claimed subject matter of instant application can be found in JAPAN 2002-198941. Therefore, the priority date of JAPAN 2002-198941 filed on 07/08/2002 can be relied upon to overcome the rejection under 35 USC 102 (a) or 102(e) as set forth below because a translation of said papers has been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Previous rejection of Claims 1-11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn because the claims have been amended.

Claims 1-3 have been cancelled, thereby renders the rejection pf claims 1-3 moot. The amended claims 4, 5, 8, and 11 no longer read on "a promoter from human telomerase" and " one E1 gene".

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 4-11 remain rejected, in part, under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of causing cytotoxicity in cancer cells comprising injection, *in vitro* or *in situ*, of a vector into a tumor comprising said cancer cells, said vector comprising the hTERT promoter operably linked to a polynucleotide comprising a gene encoding adenovirus E1A followed by an IRES and a gene encoding E1B, and for said nucleic acid, **does not** reasonably provide enablement for **1)** a method of treating cancer *in vivo*, or **2)** use of the claimed nucleic acid wherein the E1 gene is not operably linked to a promoter to cause expression. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant's arguments filed 09/14/2007 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 4-8 of the office action mailed on 06/19/2007.

The rejection is maintained in part for reasons of record set forth....The aspect of the rejection regarding a polynucleotide comprising a promoter from any human telomerase gene is ***withdrawn*** in light of Applicant's amendments to the claims.

Applicant's arguments

With respect to the aspect of the rejection regarding the breadth of the claims relating to a method of non-invasive immunization in an animal, Applicant argues the following: **(I)** Claims 1-3 have been canceled, thereby rendering the rejection moot as to these claims; **(II)** Claim 4 has been amended to recite "A polynucleotide comprising an hTERT promoter, an E1A gene, an IRES sequence, and an E1B gene in this order." Applicant argues that in view of the guidance provided by the specification, a person of ordinary skill in the art would not require undue experimentation to manufacture the polynucleotide of claim 4; **(III)** Claims 8 and 11 have been amended to recite a method comprising a distinct step (i.e., step (a)). Applicant indicates that support for these amendments is found throughout the specification, for example, in the published application (U.S. Patent Publ. No. 2006/0239967) at paragraphs 0017, 0041, 0039-0049, and in Example 6. In view of the claim amendments, and further in view of the cited disclosure, Applicant argues that a person of ordinary skill in the art would be able to carry out the claimed method without undue experimentation because adequate guidance is provided both

in the description and by way of working examples; **(IV)** Applicant further argues that the claimed oncolytic virus is capable of replicating selectively in tumor cells and inducing tumor cell death without requiring the further expression of a different therapeutic gene. Applicant states that, in other words, the present invention kills tumor cells using an entirely different mechanism, i.e., the proliferation of the virus per se within a tumor cell resulting in tumor cell death. The claimed method does not require additional desired (therapeutic) genes to be expressed to induce cell death. For this reason, i.e., because the expression of the claimed virus within a tumor cell will kill the tumor cell without the need for the expression of a therapeutic gene, the claimed invention is not subject to the same difficulties as those disclosed in the cited references. Furthermore, Applicant argues that because of these different mechanisms, the cited references are not applicable to the claimed method; and the present claims are enabled based on the present disclosure, which includes working examples (e.g., Example 6) and guidance on administration doses (see ¶ 0044). Applicant states that undue experimentation would therefore not be required to carry out the claimed method, which is distinct from the methods disclosed in the cited references on gene therapy.

In addition to above arguments, Applicant further argues that the specification provides adequate guidance how the recited virus is to be used for treating a cancer. Regarding **(i)** the genes that are to be expressed by the hTERT promoter, Applicant argues that the gene (cassette) to be expressed by the hTERT promoter is an E1A gene, IRES sequence, and an E1B gene in this order (see specification, ¶¶ 0023, 0027, and 0030). Regarding **(ii)** the routes of administration of the recited virus, Applicant argues that the routes of administration are disclosed in ¶ 0041 and Example 6. Regarding **(iii)** the technical considerations required for initiation of the expression

of a given therapeutic gene of interest and sustenance of sufficient expression level for treating a given cancer of interest, Applicant argues that the claimed method does not require the expression of a therapeutic gene (as discussed supra). Regarding **(iv)** how the immune responses resulting from introduction of adenovirus are minimized in terms of what part of adenovirus genome of the recited adenovirus remains in addition to the recited E1 gene, Applicant argues that any known suitable immunosuppressant can be used (see, e.g., ¶ 0045).

Response to Applicant's arguments

In the Non-Final office action dated 06/19/2007, three aspects of the claimed methods are considered as not enabled: 1) a method of treating cancer *in vivo*, 2) a polynucleotide comprising a promoter from any human telomerase gene or 3) use of the claimed nucleic acid wherein the E1 gene is not operably linked to a promoter to cause expression.

The Examiner acknowledges that the cancellation of claims 1-3 has rendered the rejection moot to these claims. It is also noted that claim 4 now reads as follows: A polynucleotide cassette comprising an hTERT promoter, an E1A gene, an IRES sequence, and an E1B gene in this order. Reciting "an hTERT promoter" in amended claim 4 overcomes the aspect of the rejection regarding the breadth of telomerase gene promoters encompassed by the claims. It is noted that human telomerase reverse transcriptase (hTERT) is the catalytic subunit of the human telomerase.

With respect to the aspect of the rejection regarding the lack of any active method steps in claims 8 and 11, the Examiner acknowledges that claims 8 and 11 have been amended to include a step to recite comprising the step of (a) administering an effective amount of the recombinant virus according to claim 5 (recited in claim 8, or claim 7 recited in claim 11) to a

patient in need thereof, such that the recombinant virus is capable of replicating in a tumor cell of the patient, and wherein replication of the recombinant virus kills the tumor cell.

With regard to the abovementioned claimed method considered non-enabled embodiments for the aspects of 1) a method of treating cancer *in vivo*, or 3) the use of the claimed nucleic acid wherein the E1 gene is not operably linked to a promoter to cause expression, Applicant's key argument is that *the claimed method does not require additional desired (therapeutic) genes to be expressed to induce cell death*. Accordingly, the claimed invention is not subject to the same difficulties as those disclosed in the cited references because the expression of the claimed virus within a tumor cell will kill the tumor cell without the need for the expression of a therapeutic gene. Specifically, Applicant cited Example 6 as a working example. The Examiner notes that in Example 6 the adenovirus vector (Ad-**p53**) was injected intratumorly and locally to the human lung cancer cell H1358 transplanted subcutaneously into the back of nude mice. Based on commonly accepted nomenclature in the adenovirus literature, the recited adenovirus vector (Ad-p53) refers to the adenovirus vector expresses the well-established tumor suppressor gene p53 (a desired therapeutic gene). Example 6 does not provide any evidence and/or arguments that the anticancer activity on the transplanted human lung cancer cell H1358 in nude mice after administration of Ad-p53 is the result of the expression of adenoviral E1A gene, rather than the expression of p53. Accordingly, the anticancer activity observed in Example 6 cannot be definitively attributed to the injection of the polynucleotide cassette comprising an hTERT promoter, an E1A gene, an IRES sequence, and an E1B gene in this order, as recited in amended claim 4, and its dependent claims 5-11.

Furthermore, as discussed on page 6-7 of the Non-Final office action dated 06/19/2007, the specification teaches administration of the claimed vector to cells *in vitro* and tumors implanted in mice (i.e. in situ), resulting in cytotoxicity of the cancer cells. However, the specification does not teach treatment of a cancer in a patient, i.e. *in vivo*, as recited in the step of claim 8. Accordingly, there is lack of predictability in the art regarding transport of a polynucleotide, which encodes a polypeptide of therapeutic interest (including Ad-p53 used in Example 6). For instance, the route of administration to targeted cells of certain tissue, the degradation of the administered adenoviral vector *in vivo*, the transport of polynucleotide into nucleus for transcription to occur, and the initial and sustained expression level required for desired therapeutic effects are among those critical factors need to be addressed for gene therapy, even in the case when expression of adenoviral E1A gene by the vector itself is concerned. In the absence of information disclosed regarding specific polynucleotide for certain targeted gene therapy purpose, a skilled person in the art cannot make and use of the gene therapy approach for treating a cancer without undue experimentation. As discussed on page 6-7 of the Non-Final office action dated 06/19/2007, it is unpredictable regarding whether the conditions work for a specific polynucleotide encoding a particular polypeptide may be directly extrapolate to another polynucleotide encoding another polypeptide to achieve the therapeutic effect of interest, which is encompassed by the scope of claims 8-11 of instant application, and the intended use of the polynucleotide as an anticancer recited in claim 4-7 of instant application.

In conclusion, the specification only discloses infecting cancer cells that are transplanted into a mouse (Example 6), which is not equivalent to treating a cancer in a mammal. Moreover, the specification does not disclose that E1 alone will kill the cells. Furthermore, the specification

does not disclose how one would administer the vector to a patient to treat cancer as discussed in the prior arts other than administration of the claimed vector to cells in vitro and tumors implanted in mice (i.e. in situ).

In view of the state of the art, the unpredictability in the art (as discussed on pages 4-8 of the Non-Final office action dated 06/19/2007), and the lack of specific guidance and working examples in the specification (as discussed on pages 4-8 of the Non-Final office action dated 06/19/2007, and further elaborated above), one of skill in the art would have to perform undue experimentation to make and use the claimed invention commensurate in scope with the claims as recited in claims 4-11.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Previous rejection of claims 1-3, 5-8 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Morin et al. (Morin et al., 2000, WO 00/46355, international publication date,

August 10, 2000; this reference is disclosed in IDS filed on 04/25/2006, listed as reference No. BA), is ***withdrawn*** because the claims have been amended.

Claims 1-3 have been cancelled, thereby renders the rejection pf claims 1-3 moot.

Claim 5 is amended as a dependent claim of claim 4. Claim 4 reads as follows: A polynucleotide cassette comprising an hTERT promoter, an E1A gene, an IRES sequence, and an E1B gene in this order. Reciting "an hTERT promoter". Claims 6 and 7 depend from claim 5. Claims 8 and 11, a method of treating cancer, have been amended to include a step to recite comprising the step of (a) administering an effective amount of the recombinant virus according to claim 5 (recited in claim 8, or claim 7 recited in claim 11) to a patient in need thereof, such that the recombinant virus is capable of replicating in a tumor cell of the patient, and wherein replication of the recombinant virus kills the tumor cell.

Morin et al. do not teach the limitation the amended claim 4 regarding hTERT promoter, an E1A gene, an IRES sequence, and an E1B gene arranged in this order.

5. Previous rejection of claims 1-3 and 5-11 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Cheng et al. (Cheng et al., U.S. patent application No. 2003/0104625, publication date, June 5, 2003; filed Feb. 22, 2002), is ***withdrawn*** because the claims have been amended.

Claims 1-3 have been cancelled, thereby renders the rejection pf claims 1-3 moot.

Claim 5 is amended as a dependent claim of claim 4. Claim 4 reads as follows: A polynucleotide cassette comprising an hTERT promoter, an E1A gene, an IRES sequence, and an E1B gene in this order. Reciting "an hTERT promoter". Claims 6 and 7 depend from claim

5. Claims 8 and 11, a method of treating cancer, have been amended to include a step to recite comprising the step of (a) administering an effective amount of the recombinant virus according to claim 5 (recited in claim 8, or claim 7 recited in claim 11) to a patient in need thereof, such that the recombinant virus is capable of replicating in a tumor cell of the patient, and wherein replication of the recombinant virus kills the tumor cell. Claim 9 depends from claim 8.

The Examiner notes that the publication date of Cheng et al. is 06/05/2003, which is later than the claimed priority date of JAPAN 2002-198941 filed on 07/08/2002 (with certified English translation provided on 09/14/2007). Thereby, Cheng et al. is disqualified as a 102(a) art. Nevertheless, the filing date of Cheng et al. is 02/22/2002, which is earlier than the claimed priority date of JAPAN 2002-198941 filed on 07/08/2002 (with certified English translation). Thereby, Cheng et al. remains qualified as a 102(e) art.

However, Cheng et al. do not teach the limitation the amended claim 4 regarding hTERT promoter, an E1A gene, an IRES sequence, and an E1B gene arranged in this order.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 4 as amended remain rejected, and claims 5-8 and 11 previously rejected under 35 U.S.C. 102(b) as being anticipated by Morin et al., are rejected under 35 U.S.C. 103(a) as being

unpatentable over Morin et al. (Morin et al., 2000, WO 00/46355, international publication date, August 10, 2000; this reference is disclosed in IDS filed on 04/25/2006, listed as reference No. BA) taken with Li et al. (Li et al., A hepatocellular carcinoma-specific adenovirus variant, CV890, eliminates distant human liver tumors in combination with doxorubicin. *Cancer Res.* 61(17): 6428-36, 2001; this reference is disclosed in IDS filed on 04/25/2006, listed as reference No. CC). Previous rejection is ***maintained*** for the reasons of record advanced on pages 12-14 of the Non-Final office action mailed on 06/19/06.

Claim 1 has been canceled, thereby rendering the previous rejection of claim 1 moot.

For completeness and clarity of this office action, the rejection for the reasons of record advanced on pages 12-14 of the Non-Final office action mailed on 06/19/06, is reiterated below, with edited text underlined.

Morin et al., 2000 disclosed that telomerase reverse transcriptase is part of the telomerase complex responsible for maintaining telomere length and increasing the replicative capacity of progenitor cells. Telomerase activity is turned off in mature differentiated cells, but is turned back on again in hyperplastic diseases, including many cancers. The disclosure by Morin et al., 2000 provides regulatory elements that promote transcription in cells that express telomerase reverse transcriptase (TERT). Morin et al., 2000 also described oncolytic viruses, in which a toxin or a genetic element essential for viral replication is placed under control of the TERT promoter. Thereby, the virus replicates preferentially in cells expressing TERT, and selectively lyses cancer cells (See *in vitro* Example 4 on transfected human cell lines, pages 35-36, and *in situ* Example 3 on transplanted human tumor 143B cells on nude mice, page 35).

With regard to adenovirus, adenovirus derived E1 gene, and human telomerase reverse transcriptase (TERT) promoter, Morin et al., 2000 teach a series of constructs showing construction of oncolytic adenovirus, made conditionally replicative by placing the E1a replication under control of an hTERT promoter (See lines 14-15, page 4, and Figure 5, Morin et al., 2000).

However, Morin et al. do not teach an adenovirus with IRES inserted between E1A and E1B in an adenovirus as recited in claim 4 of instant application.

At the time the claimed invention was made, the bicirtronic cassette in an adenovirus 5 vector (Ad5), E1A-IRES (internal ribosome entry site)-E1B, was known in the art for translational control of E1A and E1B expression. For instance, Li et al. devised a strategy for the control an artificial **E1A-IRES-E1B** bicistronic cassette in an adenovirus 5 vector (Ad5) and constructed an hepatocellular carcinoma (HCC)-specific oncolytic adenoviruses, CV890. CV890 efficiently replicates in and destroys AFP-producing HCC cells as well as wild-type Ad5, but replication is highly attenuated in non-AFP-producing HCC cells or non-HCC cells (See abstract, Li et al., 2001).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Morin et al., regarding the tumor cell and tissue specificity of hTERT promoter and its transcriptional regulation in an adenovirus with the teachings of Li et al. regarding a bicistronic cassette in an adenovirus 5 vector (Ad5) harboring E1A gene, an IRES sequence, and an E1B arranged in E1A-IRES-E1B order and the translational regulation by IRES. One having ordinary skill in the art would have been motivated to combine the teachings of Morin et al and Li et al. because hTERT promoter taught

by Morin et al. activate transcription in specifically in tumor cells, and IRES taught by Li et al. in an Ad5 vector controlling the expression of E1A and E1B at translational level.

There would have been a reasonable expectation of success given (i) successful identification human TERT promoter and demonstration of hTERT promoter driven reporter gene expression at transcription level by the teachings of Morin et al. and (ii) the successful construction and expression from the E1A-IRES-E1B construct by the teachings of Li et al., and its translational regulation of E1A and E1B expression exerted by IRES

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments

Applicant argues that for a claim to be obvious under 35 U.S.C. § 103, three criteria must be satisfied: i) there must be some suggestion or motivation to combine or modify the cited references; ii) there must be a reasonable expectation of success of combining or modifying the cited references; and iii) the combined references must teach each and every limitation of the claimed invention. Brown & WiUiamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000). Applicants submit that in contrast to the Examiner's position, there would have been no motivation to alter the teachings of Morin and Li to arrive at the claimed invention.

Applicant further argues that Morin et al. does not teach or suggest the claimed polynucleotide cassette with IRES inserted between E1A and E1B. Therefore, the skilled artisan would not have been motivated to insert IRES between E1A and Elb, as presently claimed. Additionally, Applicant argues that Li et al. do not disclose or suggest using hTERT

promoter such as described in Morin. Even if a skilled artisan reading Li et al. decided to replace the AFP TRE with a different promoter, there would have been no reasonable expectation that specifically replacing AFP TRE with hTERT would be successful, or any expectation that such a replacement would be advantageous, particularly in view of the large number of potential promoters that could be utilized in such a system. In other words, there is no particular teaching in Li et al. that would have lead a skilled artisan to specifically replace the AFP TRE with the hTERT promoter disclosed in Morin; a skilled artisan would have had no motivation to make such a replacement based on these two references alone.

Applicant further argues that the claimed polynucleotide results in unexpected and advantageous effects that would not have been predicted by a person of ordinary skill in the art. Specifically, the hepatocellular carcinoma (HCC)-specific oncolytic adenoviruses taught by Li et al. replicate only in specific types of cancer cells. In contrast, the claimed virus can be successfully utilized in a variety of different cancer cell types, wherein cell death is induced. Thus, Applicant argues that the claimed virus can be used in the treatment of several different cancer types. Such an advantage is not suggested by the cited references.

Response to Applicant's arguments

With regard to the argument that Morin et al. does not teach or suggest the claimed polynucleotide cassette with IRES inserted between E1A and E1B, therefore, the skilled artisan would not have been motivated to insert IRES between E1A and E1B, as presently claimed, the Examiner notes that Li et al. is the reference that taught an adenovirus with the a bicistronic cassette in an adenovirus 5 vector (Ad5) harboring E1A gene, an IRES sequence, and an E1B

arranged **in E1A-IRES-E1B order** and the translational regulation by IRES, whereas Morin et al. taught hTERT as a tumor tissue specific promoter. As stated on page 14 of the Non-Final office action dated 06/19/2007 and reiterated above in this office action, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Morin et al., regarding the tumor cell and tissue specificity of hTERT promoter and its transcriptional regulation in an adenovirus with the teachings of Li et al. regarding a bicistronic cassette in an adenovirus 5 vector (Ad5) harboring E1A gene, an IRES sequence, and an E1B arranged in E1A-IRES-E1B order and the translational regulation by IRES. One having ordinary skill in the art would have been motivated to combine the teachings of Morin et al and Li et al. because hTERT promoter taught by Morin et al. activate transcription in specifically in tumor cells, and IRES taught by Li et al. in an Ad5 vector controlling the expression of E1A and E1B at translational level.

With regard to the arguments that the claimed polynucleotide results in unexpected and advantageous effects that would not have been predicted by a person of ordinary skill in the art, it is noted that Morin et al., disclosed the tumor cell and tissue specificity of hTERT promoter and its transcriptional up-regulation in cancer cells, and Li et al. disclosed an adenovirus with the a bicistronic cassette in an adenovirus 5 vector (Ad5) harboring E1A gene, an IRES sequence, and an E1B arranged in E1A-IRES-E1B order and the translational regulation by IRES. It would have been predicted by a person of ordinary skill with a reasonable expectation of success for claimed polynucleotide and its use in treating cancer ***in vitro***, as encompassed by the breadth of the claims of instant application given (i) the successful identification human TERT promoter and demonstration of hTERT promoter driven reporter gene expression at transcription level in

tumor cells, by the teachings of Morin et al. and (ii) the successful construction and expression from the E1A-IRES-E1B construct to cause death of a specific desired cell type give the use of a tissue-specific promoter by the teachings of Li et al., and its translational regulation of E1A and E1B expression exerted, by IRES. Thus, combination of the teachings of Morin et al. and of Li et al. to arrive at the claimed invention requires only the substitution of a tissue-specific promoter that leads to expression in a desired specific cell type.

Furthermore, with regard to the asserted requirement for teaching, suggestion, or motivation to render obviousness, the Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). The Examiner also notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.*, the suggestion and motivation to combine Morin et al. 2000 and Li et al., 2001 has been clearly set forth on pages 12-14 of the Non-Final office action mailed on 03/05/2007, and reiterated above in this office action.

Conclusion

7. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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